REMARKS

Amendments

Claim 1 is amended to provide concordance with the preamble. Claim 11 is amended to provide art-recognized full names corresponding to the acronym terms-of-art. These amendments do not change the scope or meaning of the claims, and introduce no new matter.

IDS

The IDS received Apr 02, 2004 was not filed by the Applicant, nor their agent, and does not belong in this file. Our serial number was erroneously placed on an IDS filed by another attorney from another law firm in an unrelated application. Please remove these documents from our file.

35USC112, second paragraph

Claims 9 and 12-20 require that the recited protease be native to the membrane. As noted in the Specification, the recited protease is generally native to the membrane preparation of the sample; LDL receptors are known to be naturally expressed in a wide variety of cell types, and we find that cellular membranes of these cells generally provide assay-usable protease activity (Specification, p.5, lines 3-5; see also, Table 1 and Experimental Procedures).

Step a) of claim 1 requires a sample comprising a cell membrane comprising (i) a polypeptide comprising an LDL receptor transmembrane domain fused to a C-terminal tail, and (ii) a protease which specifically cleaves the domain and thereby releases the tail from the membrane. Claims 9 and 12-20 further require that the recited protease be native to the membrane; i.e. it is not provided from an exogenous source, but it is native to, and already present in the recited cell membrane.

35USC102(b)

Willnow et al. (1994, J Biol Chem 269, 15827-32) describe the production and functional analysis of truncated LRPs comprising subsets of the of the native N-terminal, extracellular domains (Fig. 1). One minireceptor was partially cleaved at a known region IV proteolytic processing site (Fig. 2A, lanes 2 and 4). LRP is known to be naturally protcolyzed at this

extracellular N-terminal proteolytic processing site to generate two subunits: a 85 kd membrane spanning beta subunit, and a larger 515 kd N-terminal alpha-subunit which lacks a membrane-spanning region, but remains attached to the membrane through noncovalent association with the smaller C-terminal beta-subunit (Herz et al. (1990, EMBO J 9, 1769-1776).

The present inventors disclose that LRP and other members of the LDL receptor gene family undergo distinct endoproteolytic processing events *that result in the release of their cytoplasmic tails into the cytoplasm*. Specification, p.1, liens 24-26. To release a cytoplasmic tail, the disclosed processing need to occur at intramembranous or cytoplasmic sites – not the N-terminal, extracellular region IV processing site known in the art, which liberates an extracellular domain, and not a cytoplasmic tail.

Accordingly, all our claimed methods are for detecting proteolysis of an LDL receptor transmembrane domain, and require a cell membrane comprising (i) a polypeptide comprising an LDL receptor transmembrane domain fused to a C-terminal tail, and (ii) a protease which specifically cleaves the domain and thereby releases the tail from the membrane. In contrast, Willnow describes an LRP which is cleaved at an N-terminal, extracellular site, and does not and cannot release from the membrane any C-terminal tail.

35USC102(a)

Kinoshita (Nov 1, 2001, J Neurosci 21, 8354-61) describes how APP is known to be cleaved by α- or β-secretases, releasing the ectodomain of APP (soluble APP) and membrane-bound C-terminal fragments. Konishita demonstrates interaction between the extracellular domains of APP and LRP. However, nowhere does Konishita suggest that LRP is even capable of proteolytically liberating a C-terminal tail, so Konishita does not and cannot disclose or suggest producing and detecting a protease liberated C-terminal tail of LRP as required by our claims. In any event, we do not understand why this reference is cited under 35USC102(a), since it is dated Nov 1, 2001 – after our filing date, and hence would not appear to be prior art.

35USC103(a)

Willnow and Kinoshita have been described above. Herz (2001, Neuron 29, 571-81) describes LDL receptor family proteins, and reviews the diverse physiological roles that these receptors have been found to play. However, nowhere does Herz disclose or suggest producing and detecting a protease liberated C-terminal tail of any LDR receptor as required by our claims.

The Examiner is invited to call the undersigned if he would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

We petition for and authorize charging our Deposit Account No.19-0750 all necessary extensions of time. The Commissioner is authorized to charge any fees or credit any overcharges relating to this communication to our Dep. Acct. No.19-0750 (order UTSD:0862).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP

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